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ARTICLE

Electrophilic iodine(I) compounds induced semipinacol rearrangement via C–X bond cleavage

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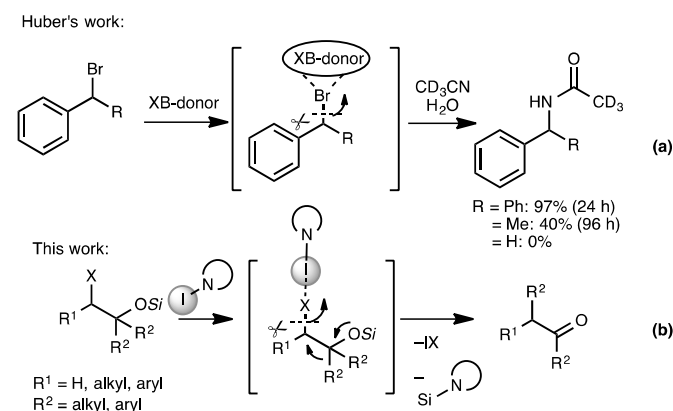
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Neutral electrophilic iodine(I) species proved to be efficient reagents for C–X bond cleavage of various cyclic and acyclic α -silyloxyhalides, and the induced desilylative semipinacol rearrangement provided the corresponding ketones in good yields. The reaction is operationally simple, and proceeds under mild conditions with good functional group compatibility. Mechanistic investigations, including computational studies, were also performed.

Alkyl halides are one of the most fundamental synthetic intermediates in organic synthesis, and have been used for a variety of bond-forming reactions via halide abstraction by halophilic Lewis acids, such as Ag, Mg, Zn, and In.^{1–4} Recently, Huber *et al.* reported that a non-metallic multidentate iodoimidazolium salt could be used for C–Br bond cleavage of benzylic bromides, promoting a Ritter-type reaction (Scheme 1a).⁵ They reported that the reaction was driven by “halogen bond”, i.e., the interaction between an electron-deficient iodine atom and a Lewis base.⁶ They also achieved the same reaction using iodoimidazolium⁷ and iodopyridinium salts⁸ as halogen bond donors. The same group also reported the first halogen bond donor-catalyzed nucleophilic substitution of 1-chloroisochroman using catalytic amounts of electron-deficient multidentate iodoarenes as halogen bond donors.⁹ Although the existence of halogen bond has been known for more than a century,¹⁰ almost all research has been conducted in the fields of supramolecular chemistry and crystal engineering.¹¹ Only a few reactions involving halogen bond as the driving force have been reported in the field of synthetic chemistry,^{12–15} and the two reactions described above are the only examples involving cleavage of C–X bonds.⁵

These pioneering studies showed the potential use of halogen bond in synthetic chemistry, but the field is still in its infancy because of its limited scope and reactions. Although Huber’s halogen bond donor reagent unambiguously induces C–X bond cleavage with reactive benzylic bromides, the yields depend on the choice of substrate so strongly that a primary benzylic

bromide did not provide any of the desired amide. We became curious as to whether this intriguing interaction could be strong enough to activate such unreactive C–X bonds as non-benzylic halides or primary halides. We envisaged that complete charge transfer from the alkyl halide to iodine(I) compounds could promote this transformation; highly electrophilic iodine(I) species could activate such C–X bonds to afford a reactive carbocation intermediate, simultaneously forming a covalent I–X bond (Scheme 1b).



Scheme 1. Reactions induced by halide abstraction

In this paper we report an electrophilic iodine(I)-promoted semipinacol rearrangement using *N*-iodosuccinimide (NIS) and *N*-iodosaccharin (NISac) as halogen bond donors.¹⁶ To the best of our knowledge, there has been no previous report showing that readily available NIS or NISac are efficient reagents for activation of the C–X bond of an alkyl halide.

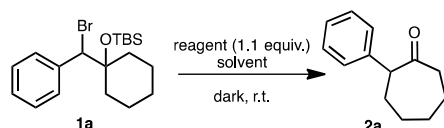
We started the investigation with alkyl bromide **1a** (Table 1). We first tried commercially available electron-deficient iodoarenes and perfluoroiodoalkanes, but none of these afforded the desired compound (entries 1–4). The

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iodoimidazolium salt **4**, which has an electron-deficient iodine atom, was also examined, but no reaction was observed under these conditions (entry 5). These results indicated that there is only insufficient interaction between these electron-deficient iodine atoms and alkyl halides. We then examined various electrophilic iodine(I) compounds, including NIS,¹⁷ NISac (**5**),¹⁸ and Barluenga's reagent (**6**), and they proved to be efficient reagents for this transformation (entries 6–8). NIS promoted the desired rearrangement to afford **2a** in 72% yield. When NISac was used, **1a** was consumed in only 15 min but the yield of **2a** decreased slightly. With Barluenga's reagent (**6**), the reaction proceeded sluggishly and the yield was lower. *N*-bromosuccinimide (NBS) did not provide any rearranged product (entry 9). Molecular iodine, succinimide, and tetrabutylammonium iodide (TBAI) were also examined, but none of them induced the rearrangement (entries 10–12). These control experiments suggest that neither molecular iodine nor iodide is capable of promoting this reaction, and that the electrophilic iodine(I) compounds themselves are the active species.

Table 1. Optimization of reaction conditions



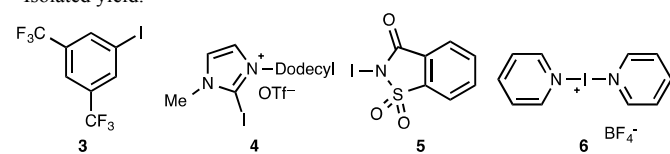
Entry	Reagent	Solvent	Time (h)	Yield (%) ^a
1	<i>n</i> -C ₈ F ₁₇ I	CH ₂ Cl ₂	24	n.d. ^b
2	<i>n</i> -C ₁₀ F ₂₁ I	CH ₂ Cl ₂	24	n.d. ^b
3	C ₆ F ₅ I	CH ₂ Cl ₂	24	n.d. ^b
4	3	CH ₂ Cl ₂	24	n.d. ^b
5	4	CH ₂ Cl ₂	24	n.d. ^b
6	NIS	CH ₂ Cl ₂	8.5 ^c	72
7	NISac (5)	CH ₂ Cl ₂	15 min ^c	62
8	6	CH ₂ Cl ₂	48	58
9	NBS	CH ₂ Cl ₂	24	n.d. ^b
10	I ₂	CH ₂ Cl ₂	24	n.d. ^b
11	succinimide	CH ₂ Cl ₂	24	n.d. ^b
12	TBAI	CH ₂ Cl ₂	24	n.d. ^b
13	NIS	MeCN	18 ^c	30
14	NIS	MeNO ₂	40 min ^c	75 (69 ^d)
15	NIS	EtNO ₂	5.5 ^c	45

^a NMR yields based on dimethylsulfone as an internal standard.

^b Not detected.

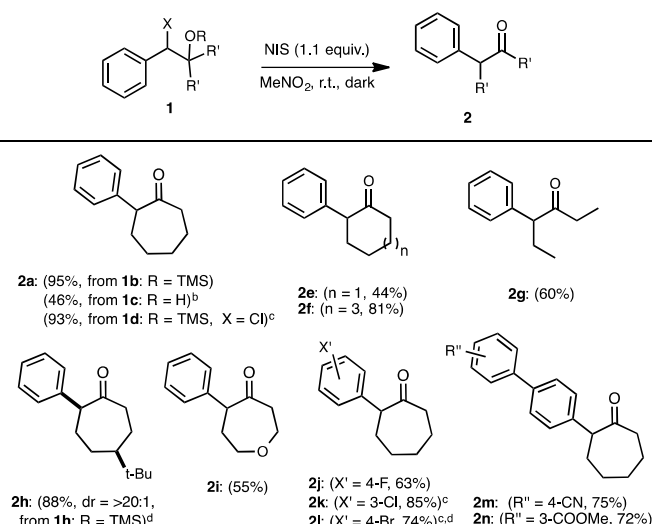
^c Reaction mixture was stirred until consumption of **1a**.

^d Isolated yield.



The choice of solvent also turned out to be crucial (entries 13–15). The reaction in nitromethane gave **2a** more rapidly and in a better yield than that in dichloromethane. Acetonitrile and nitroethane provided **2a** but the yields were low. None of the other polar and non-polar solvents investigated afforded **2a**, presumably because of their reactivity toward NIS, or the insolubility of NIS in them.

Table 2. Scope and limitation^a



^a Unless otherwise noted, R = TBS, X = Br.

^b NMR yields based on dimethylsulfone as an internal standard.

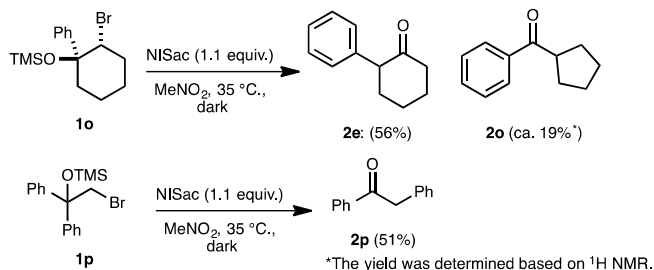
^c The reaction was conducted at 35 °C.

^d The reaction was performed in MeNO₂/CH₂Cl₂ (2:1).

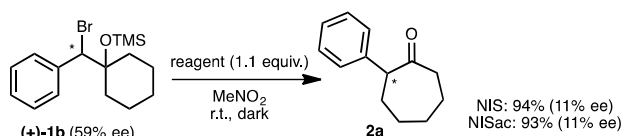
With the optimized conditions in hand, the reaction scope and limitations were examined (Table 2). Substrate **1b**, bearing a trimethylsilyl group, afforded the desired product **2a** in excellent yield, but the unprotected haloether **1c** gave **2a** in a lower yield. It is worth noting that C–Cl bond activation of **1d** successfully provided the rearranged product **1a** in 93% yield. The cyclohexanone **2e**, cyclooctanone **2f**, and even acyclic ketone **2g** were also obtained in moderate to good yields. When substrate **1h** bearing a *tert*-butyl group on the cyclohexane ring was employed, the reaction took place to afford **2h** in a highly diastereoselective manner.¹⁹ The tetrahydropyran derivative, bearing a Lewis basic oxygen atom, also yielded the rearranged product **2i** in moderate yield. Notably, various substituents on aromatic rings, including fluoride, chloride, bromide, cyanide, and methoxycarbonyl groups, were compatible with the reaction conditions, affording the corresponding ketones **2j–n** in 63–85% yields.

We then thought that less reactive alkyl halides could be activated by NISac (**5**), which has stronger Lewis acidity than NIS, according to Table 1. As expected, **5** promoted the rearrangement of secondary bromide **1o** and primary bromide **1p**, albeit in moderate yields (Scheme 2). Interestingly, the rearrangement of **1o** afforded **2e** as a major product despite the fact that **2o** would be obtained if the reaction proceeds in a

concerted manner.²⁰ At this point, we assumed that our reaction proceeded via a carbocation intermediate. To verify this hypothesis, we examined the reaction using chiral substrate **1b** (Scheme 3). NIS- and NISac-mediated semipinacol rearrangements of chiral **1a** provided **2a** in excellent yields, but the enantiomeric excess dropped to 11%.²¹ These results suggest that the iodine (I) compounds induced reaction proceeded mainly in a stepwise manner, via a benzylic carbocation intermediate.²²



Scheme 2. NISac-induced semipinacol rearrangements



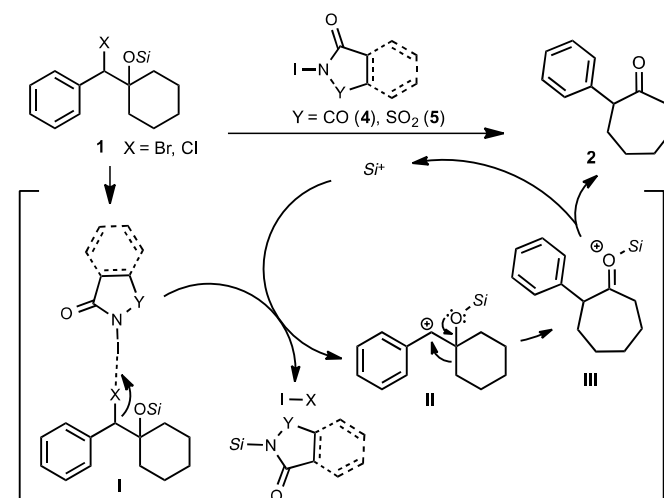
Scheme 3. Racemization of benzylic carbon

A plausible reaction mechanism is shown in Scheme 4. First, the interaction between the alkyl halide and halophilic Lewis acid activates the C–X bond (**I**). Subsequent release of iodine halide and silylated counter anion affords carbocation **II**, which can undergo 1,2-alkyl migration to provide oxonium cation **III**. Finally, desilylation of **III** yields the rearranged product **2**.

Several experiments were conducted to gain further insights into the reaction mechanism. When the reaction was performed under visible light the reproducibility was poor; this result supports the idea that the main reaction process does not involve an iodine radical. The radical mechanism can also be discounted because a catalytic amount of NIS or NISac was unable to send this reaction to completion, even after 24 h. Additionally, we detected MS signals of IBr_2^- (286.7) and I_2Br^- (334.7) from the crude reaction mixture of **1a**; these are detected in iodine bromide solutions in dichloromethane.²³

Finally, to evaluate Lewis acidity of NIS and NISac, the maximum electrostatic potential (ESP) energy surface was calculated and compared with those of several organoiodine compounds,²⁴ since the values ($V_{s,\text{max}}$) are reported to have relationship with the Lewis acidity of the electron-deficient organoiodine compounds (termed as σ -hole).^{6a,b,25} As expected, the results correlated closely with the experimental data, as shown in Table 1; the order of the maximum values was $\text{NISac} > \text{iodoimidazolium triflate} > \text{NIS} > \text{IBr} > n\text{-C}_8\text{F}_{17}\text{I} > \text{C}_6\text{F}_5\text{I}$, $\text{NBS} > \text{I}_2$. Iodoimidazolium triflate did not promote the rearrangement of **1**, despite its relatively high value, suggesting that complete charge transfer from the bromine atom of **1** to the

iodine atom on reagents such as NIS and NISac is vital for the rearrangement of **1**; this step would be the driving force of the reaction.



Scheme 4. Plausible reaction mechanism

In conclusion, we developed a novel NIS- and NISac-induced desilylative semipinacol rearrangement of various halohydrin silyl ethers. Not only reactive benzyl bromides, but also less reactive benzyl chlorides, non-benzylic secondary bromides, and even primary bromides afforded the rearranged product. The experimental results suggest that the reaction proceeds predominantly via a carbocation intermediate through XB-mediated C–X bond activation. Computational studies indicated that N–I bond cleavage of NIS and NISac should facilitate the X–I covalent bond formation, promoting the subsequent rearrangement. Our results open a new door to electrophilic iodine(I) species promoted and catalyzed reactions through C–X bond activation.²⁶

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